IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Francisco Sanchez-Madrid, *et al.*		
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FOR:	Immune Regulation Based On The Targeting Of Early Activation Molecules		

Via EFS
Commissioner for Patents
P.O. Box 1450
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Statement of Substance of Examiner Interview

Applicants' representative would like to thank the Examiner for the courtesies extended during the interview conducted on December 17, 2009. The rejections set forth under the issues raised in the Office Action mailed with respect to 35 U.S.C. § 103(a) were discussed during the interview. A summary follows.

Applicants' representative emphasized that the claims are directed to a method of treating rheumatoid arthritis with an depleting anti-CD69 antibody and that none of the references cited in the Office Action expressly teach a CD69 depleting antibody, let alone any method for using such an antibody. Further, the primary reference Choy 1998[1/] expressly teaches that no depleting antibody should be used for treating rheumatoid arthritis, but rather non-depleting antibodies should be used as part of "a strategy aiming to tolerize T cells" as "non-depleting anti-CD4 monoclonal antibodies in rheumatoid arthritis showed that they could suppress synovitis."[2/] Applicants' representative emphasized that the teaching away in Choy 1998 from using depleting antibodies is made expressly clear and teaches that the negative effects seen with the use of

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1/ Choy *et al.*, Br J Rheumatol. 1998 May;37(5):484-90. Review.

2/ See Choy 1998 at Abstract.

depleting anti-CD4 antibody "**is likely to apply to all depleting anti-T-cell [monoclonal antibodies]**". Specifically, Choy 1998 states the following:[3/]

> Among the synovial CD4+lymphocytes, most are recruited non-specifically to the joint and only a small proportion are the disease driving arthritogenic lymphocytes. Therefore, if one aims to improve arthritis by depleting synovial CD4+lymphocytes, sufficiently high doses must be given to achieve significant concentration in the joint. However, at these doses of depleting mAbs, there may be severe depletion of peripheral CD4+ lymphocytes for a prolonged period, resulting in an unacceptable level of immunosuppression. **This principle is likely to apply to all depleting anti-T-cell mAbs. Therefore, the T-cell-depletion strategy has been abandoned in favour of a strategy aiming to tolerize T cells.**

Applicants' representative emphasized that when McInnes 1998[4/] is read in its entirety, it becomes clear that McInnes 1998 is referring to IL-15 and/or CD4 as the targets for therapy, and particularly CD69 is never suggested as a target for therapy. Specifically, Applicants' representative directed attention to the passage of McInnes 1998 that provides, in part, as follows (emphasis added):

> [D]iverse cell types within synovial membrane may exhibit coordinate proinflammatory activities through cell contact. … T-cell-directed therapies that not only *inhibit* T-cell activation but also *deplete* T cells from the synovial compartment, or at least *interfere* with their membrane interactions, will probably be the most efficacious. It is *of interest* that clinical improvement following CD4 therapy in RA correlates with synovial T-cell coating with anti-CD4. *Citing* Choy 1996[5/].

With regard to depletion therapies referred to in the above passage, McInnes 1998 references anti-CD4 therapy and cites the reference of Choy 1996, which showed that the percentage of anti-CD4 monoclonal antibody-coated lymphocytes in the rheumatoid joint is associated with clinical improvement. Indeed, the primary reference of Choy 1998 is actually the follow-on paper to Choy 1996 detailing the results of the study that was "of interest" to McInnes 1998. As above, Choy 1998 teaches that all deletion therapies should be avoided in favor of those therapies that tolerize T-cells.

Applicants' representative emphasized that depletion therapy using an anti-CD69 antibody is never contemplated in any of the cited references. Specifically, McInnes 1997 and McInnes 1998 are concerned with elucidating the role IL-15 in rheumatoid arthritis, not

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3/ See Choy 1998 at page 488, left column, last two lines, to right column, line 12.

4/ *Immunol Today.* 1998 Feb; 19(2):75-9.

5/ Choy et al., *Arthritis Rheum.* 39, 52-56 (1996).

developing CD69 as a target. McInnes 1998 teaches IL-15 or IL-15 receptors may be targeted to *inhibit* T-cell activation and *interfere* with their membrane interactions. Specifically, McInnes 1998 teaches that "IL-15 can recruit T cells and … modify cell-cell interactions within inflammatory sites,"[6/] that IL-15 expression is associated with rheumatoid arthritis,[7/] and that "IL-15 can recruit and expand CD45R0+ memory cell subsets in the synovial membrane, in which, … newly recruited T-cells can produce TNF-α directly or via contact with macrophages."[8/] Further, McInnes 1998 concludes with the following:

> The identification of IL-15-mediated T-cell and monocyte activation in the synovial membrane, … provides a novel target for such biological approaches. This might be either through direct neutralization of IL-15 or by targeting IL-15 receptors.

At best, the combination of Choy 1998 and McInnes 1997 only suggest the use of non-depleting antibodies. The Examiner emphasized that McInnes 1997 teach that McInnes 1997 teaches that peripheral blood T-cells and U937 cells that are co-cultured in the presence of IL-15 in vitro have decreased TNFα production when treated with a non-depleting, neutralizing antibody to CD69.[9/] Applicants' representative emphasized that the antibody used in McInnes 1997 was a non-depleting, neutralizing CD69 antibody. Even assuming, arguendo, that a person of ordinary skill in the art would have been motivated[10/] to use the non-depleting, neutralizing CD69 antibody, the result is the treatment of rheumatoid arthritis with an antibody that "tolerizes T cells", as suggested by Choy 1998, with the non-depleting, neutralizing CD69 antibody disclosed by McInnes 1997. This is NOT the subject of the present claims.

Applicants' representative emphasized that the in contrast to the teachings of Choy 1998, the present specification includes data from an in vivo model for unwanted immune response that shows, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor anti-CD69 antibody, as opposed to a non-depleting or tolerizing antibody. Treatment of mice having collagen-induced arthritis (CIA) with a non-depleting CD69 specific antibody that does not

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6/ McInnes 1998 at page 76, left column, lines 32-34.

7/ McInnes 1998 at Title. See also the entire document.

8/ McInnes 1998 at page 77, left column, lines 17-20.

9/ *See* McInnes 1997 at page 193, Figure 7 legend.

10/ Applicants do not concede that their was sufficient motivation.

deplete CD69+ cells in vivo (i.e., mAb 2.2) actually exacerbated CIA in those mice.[11/] The Examiner alleged that these results were not unexpected and/or not relevant to the obviousness determination. Rather, the Examiner emphasized that Marzio[12/] teaches that CD69+ T cells may be found in the synovial fluid and synovial membrane from rheumatoid arthritis patients and that this teaching would have motivated a person of ordinary skill in the art to use a depleting CD69 antibody to treat rheumatoid arthritis. Applicants' representative emphasized that Marzio does not disclose a depleting anti-CD69 antibody and does not teach the use of any CD69 antibodies, let alone depleting anti-CD69 antibodies, to treat rheumatoid arthritis. Applicants' representative further emphasized that the weight of the evidence would not have directed a person of ordinary skill in the art to use depleting anti-CD69 antibodies to treat rheumatoid arthritis at least because Choy 1998 strongly discourages the use of depleting antibodies altogether "in favor of a strategy to tolerize T cells."[13/] Further, there is no teaching cited by the Examiner that suggests that depleting anti-CD69 antibodies would have been more suitable than antibodies that merely tolerize or neutralize T-cells. Thus, the data in the specification would have been unexpected to a person of ordinary skill in the art, at least in view of Choy 1998, because the data of the present specification suggest that a neutralizing anti-CD69 antibody may actually exacerbate an arthritic condition whereas a depletor anti-CD69 antibody alleviated an arthritic condition.

Finally, Applicants' representative emphasized that none of the references actually teach or describe a depleting anti-CD69 antibody. The Examiner explained that the references of Strom[14/] and White[15/] were cited to show that it would have been technically possible to manufacture any depleting antibody. Strom provides a general description related to agents that are target cell depleting for an interleukin- or interleukin receptor-bearing (*e.g.*, IL-2 and IL-15R) cell.[16/] White concerns the treatment of B-cell malignancies with radiolabeled anti-CD20 antibodies.[17/] Neither Strom nor White teach or suggest making any anti-CD69 antibody let alone a depleting anti-CD69 antibody of the present claims. Neither Strom nor White teach or

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11/ *See e.g.*, Specification at page 105, lines 3-6.

12/ Marzio *et al.*, Immunopharmacol Immunotoxicol. 1999 Aug; 21 (3):565-82

13/ See Choy 1998 at page 488, right column, line 12.

14/ U.S. Publication No. 2002/0114781.

15/ U.S. Publication No. 2002/0039557.

16/ Strom at paragraphs 54 and 55.

17/ White at paragraph 26.

suggest the use of any anti-CD69 antibody, let alone depleting anti-CD69 antibodies, to treat rheumatoid arthritis.

Respectfully submitted,

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